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Current approach to resistant hypertension

Çelebi Yıldırım[1], Afnan Chaudhry[1], Mohamad Talal Basrak[1], Çağrı Aksu[1], Mesut Karataş[2], Alexander M Digregorio[1]

[1]*Department of Internal Medicine, Phoenexville Hospital Towerhealth, Phoenixville, PA, USA*
[2]*Department of Cardiology, Koşuyolu Yüksek İhtisar Training and Research Hospital, İstanbul, Turkiye*

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Corresponding Author: Çelebi Yıldırım, celebi.yildirim@towerhealth.org

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ABSTRACT

Resistant hypertension is the inability to achieve target blood pressure (<130/80 mmHg) despite using the maximum tolerated doses of three antihypertensive drugs, including a diuretic, or the need for four or more medications. It is linked to aging, obesity, obstructive sleep apnea, and chronic kidney disease, with contributing factors such as high sodium intake and sympathetic nervous system overactivity. Treatment includes optimizing diuretic use, with spironolactone proving highly effective. Lifestyle modifications, including sodium reduction and exercise, are critical. Emerging therapies like renal denervation offer promising long-term blood pressure control.

Keywords: Resistant hypertension, sympathetic nervous system, diuretic, renal denervation

INTRODUCTION

Hypertension is a significant modifiable risk factor for coronary artery disease (CAD), heart failure (HF), stroke, chronic kidney disease (CKD), and dementia.[1]

According to 2017 American College of Cardiology/ American Heart Association (ACC/AHA) Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults; hypertension stage 1 is systolic blood pressure (SBP) 130-139 or DBP 80-89 mm Hg, and hypertension stage 2 is SBP ≥140 or diastolic blood pressure DBP ≥90 mm Hg[2]. The 2024 ESC Guidelines define non elevated blood pressures as SBP <120 mmHg and DBP <70, elevated blood pressures as SBP 120-139 mmHg or DBP 70-90 mmHg hypertension as a confirmed office SBP of ≥140 mmHg or DBP of ≥90 mmHg.[1]

Resistant hypertension (RH) is characterized by the inability to reach target blood pressure levels (<130/80 mmHg (average of two readings at a healthcare clinic on two different or consecutive days) or average BP of <125/75 mmHg on a 24-hour ambulatory BP monitor (ABPM)) when a patient is prescribed the highest or most tolerable doses of three antihypertensive medications from different classes, including a diuretic.[3] RH also encompasses patients whose blood pressure remains at target levels despite the use of four or more antihypertensive medications.

ETIOLOGY

RH is a prevalent issue encountered by both primary care providers and specialists. Although the precise prevalence is not well-established, clinical trials indicate that it affects an estimated 20% to 30% of participants.[4] The prevalence of RH is expected to rise due to factors such as an aging population and increasing rates of obesity, sleep apnea, and CKD.[5]

The diagnosis of RH requires ruling out "pseudo resistance" due to medication non-adherence, improper blood pressure measurement, and the white-coat effect. Measuring blood pressure accurately requires proper technique, proper cuff size, and use of validated devices.[6]

An often reason for pseudo-resistant hypertension is the insufficient dosage of antihypertensive medications or the use of inappropriate drug combinations. According to data from a specialized hypertension clinic, the most common adjustment that helped patients reach their blood pressure goals was either increasing the dosage of their medication or starting or switching to the correct diuretic.[5]

After confirming adherence to antihypertensive medications and ruling out a white-coat effect through out-of-office blood pressure measurements, the evaluation of RH involves identifying lifestyle factors contributing to the condition, detecting any drugs that might affect antihypertensive efficacy, screening for secondary causes of hypertension, and assessing for target organ damage.

Contributing factors as considered as volume expansion, overweight/obesity, exogenous substances, physical inactivity, excess daily dietary sodium, excess habitual alcohol consumption.[1] Secondary hypertension is more prevalent in individuals with RH compared to those with general hypertension. The most frequent causes of RH are hyperaldosteronism, CKD, renal artery stenosis, and

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obstructive sleep apnea (OSA). The likelihood of secondary hypertension also increases with age, primarily due to higher rates of CKD, OSA, and renal artery stenosis.[7]

In one study, it was observed that younger patients with RH presented with a significantly higher prevalence of the condition compared to older individuals. These younger patients were diagnosed with hypertension at an earlier age and exhibited a greater prevalence of obesity, OSA, elevated aldosterone levels, and higher dietary sodium intake. This distinct phenotype in younger patients underscores a more severe form of RH, driven by a combination of these risk factors, which contributes to their elevated cardiovascular risk compared to older patients.[8]

PATHOPHYSIOLOGY

Normal blood pressure is maintained through various physiological mechanisms, and disruptions in these mechanisms can lead to hypertension. RH is primarily associated with two key processes: the renin-angiotensin-aldosterone system and increased activity of the sympathetic nervous system.[9]

In patients with RH, elevated sympathetic nerve activity is thought to be the primary contributing factor.[10]

Secondary hypertension is often categorized by plasma renin activity levels, with low-renin cases involving sodium handling issues in the distal nephron, including mineralocorticoid receptor dysfunction or problems with tubular pathways like the epithelial sodium channel or sodium chloride co-transporter. Rare causes such as glucocorticoid-remediable aldosteronism and Liddle's syndrome are well-documented, primary aldosteronism is a common secondary cause, affecting 20% to 23% of patients with RH.[11] These factors cause an overload of volume and sodium, resulting in increased peripheral vascular resistance, arterial stiffness, and subsequent damage to organs due to hypertension.[12]

Several conditions contribute to these mechanisms. The most frequent causes of RH are hyperaldosteronism, CKD, renal artery stenosis, and OSA.[12]

TREATMENT

The ACC/AHA guideline suggests aiming for a blood pressure target of less than 130/80 mm Hg for all of the age groups.[2] Both the ACC/AHA and ESC guidelines recommend starting antihypertensive treatment for patients with established cardiovascular disease (CVD) and a blood pressure of 130/80 mm Hg or higher. The ACC/AHA guidelines also specify that treatment should begin for those with a 10-year risk of atherosclerotic CVD exceeding 10%.[13]

Lifestyle Modifications

Patients with RH should be advised on lifestyle changes to help reduce their blood pressure. A key factor in RH is high sodium intake. Sodium restriction has a particularly significant impact on lowering blood pressure in patients with RH. In one study, reducing sodium intake to 1.1 g/day led to a 23/9 mm Hg decrease in 24-hour ambulatory blood pressure among patients whose hypertension was not well controlled despite being on a three-drug regimen that included a diuretic.[14]

The Dietary Approaches to Stop Hypertension (DASH) diet promotes the consumption of whole grains, vegetables, fruits, and low-fat dairy products, while reducing intake of saturated fats, processed foods, and added sugars. Research has consistently shown that this dietary strategy effectively lowers blood pressure in individuals with RH. Additionally, the Mediterranean diet has been found to offer comparable benefits in managing blood pressure levels.[12,15]

For patients with hypertension, engaging in physical activity is linked to a reduced risk of CVD mortality compared to those who are sedentary. The ESC 2024 guidelines recommend at least 150 minutes of moderate-intensity aerobic exercise per week (about 30 minutes on most days, 5-7 days per week), or 75 minutes of vigorous-intensity exercise per week spread over at least 3 days. Additional benefits are observed with 300 minutes of moderate-intensity or 150 minutes of vigorous-intensity aerobic exercise per week.[1]

Medical Treatment

Pharmacological treatment for patients with RH despite a three anti-hypertensive medicine should begin with optimization of diuretic use.[14] Researches indicate that adjusting diuretic therapy—whether by introducing a new diuretic, increasing its dose, or switching types based on kidney function—can help more than 60% of patients achieve their blood pressure goals.[5,16,17]

A study revealed that chlorthalidone, a thiazide like diuretic, is at least twice as potent as hydrochlorothiazide.[18]

Spironolactone, a potent aldosterone antagonist, has shown significant efficacy in treating RH, particularly in cases where sodium retention is a primary factor. The PATHWAY-2 study demonstrated that spironolactone, when added to a three-drug regimen, reduced SBP more effectively than placebo, bisoprolol, or doxazosin. Its effectiveness is linked to its ability to counteract aldosterone's effects, and renin profiling can predict responsiveness to the drug. Despite its advantages, careful monitoring is required due to risks like hyperkalemia, especially in patients with kidney disease.[19] In a recent network meta-analysis involving 24 studies and approximately 3,000 participants, spironolactone emerged as the most effective treatment for lowering office SBP compared to other interventions.[20]

For patients who qualify for sodium-glucose cotransporter 2 inhibitors (SGLT2Is), adding these medications to existing antihypertensive therapy can provide a moderate additional reduction in blood pressure.[21]

Invasive Strategies

Sympathetic nervous system overactivity contributes to the development and progression of hypertension.[1,22,23]

Increased renal norepinephrine (NE) spillover in numerous patients with primary and RH supports the idea that renal nerves are crucial in linking heightened central sympathetic activity to impaired renal function, which contributes to chronic hypertension.[23] 2024 ESC guidelines advise considering renal denervation therapy as a supplementary or alternative treatment for patients with RH that remains uncontrolled or who suffer from side effects of medications.[1]

Long-term follow-up studies show that these BP-lowering effects can be sustained for up to 3 years, with some data suggesting benefits may last up to 10 years. This suggests a notable advantage of renal denervation: its potentially enduring impact on BP, which may appeal to patients who struggle with adherence to daily medication and prefer a single, long-lasting intervention.[24,25]

CONCLUSION

Because patients with resistant hypertension are at higher risk of complications, including cardiovascular disease, stroke, renal failure, and death, lifestyle changes, use of antihypertensive drugs with different mechanisms of action, and a stepwise approach to management should be targeted to achieve blood pressure control, as should the search for secondary causes.

REFERENCES

1. McEvoy JW, McCarthy CP, Bruno RM, et al. 2024 ESC Guidelines for the management of elevated blood pressure and hypertension. *Eur Heart J*. 2024:ehae178. doi: 10.1093/eurheartj/ehae178
2. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: a report of the American college of cardiology/American heart association task force on clinical practice guidelines. *J Am Coll Cardiol*. 2018;71(19):e127-e248. doi: 10.1016/j.jacc.2017.11.006
3. Mittal S, Jain P, Sharma R, et al. Approaches in managing resistant hypertension: a review. *Cureus*. 2024 Apr 8;16(4):e57804. doi: 10.7759/cureus.57804
4. Calhoun DA, Jones D, Textor S, et al. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American heart association professional education committee of the council for high blood pressure research. *Hypertension*. 2008;51(6):1403-19. doi: 10.1161/HYPERTENSIONAHA.108.189141
5. Sarafidis PA, Bakris GL. Resistant hypertension: an overview of evaluation and treatment. *J Am Coll Cardiol*. 2008;52(22):1749-57. doi: 10.1016/j.jacc.2008.08.036
6. Yahr J, Thomas G, Calle J, Taliercio JJ. Resistant hypertension: a stepwise approach. *Cleve Clin J Med*. 2023;90(2):115-125. doi: 10.3949/ccjm.90a.22046
7. Pimenta E, Gaddam KK, Oparil S. Mechanisms and treatment of resistant hypertension. *J Clin Hypertens (Greenwich)*. 2008;10(3):239-44. doi: 10.1111/j.1751-7176.2008.08143.x
8. Ghazi L, Oparil S, Calhoun DA, Lin CP, Dudenbostel T. Distinctive risk factors and phenotype of younger patients with resistant hypertension: age is relevant. *Hypertension*. 2017;69(5):827-835. doi: 10.1161/HYPERTENSIONAHA.116.08632
9. Bădilă E, Japie C, Weiss E, Balahura AM, Bartoș D, Scafa Udriște A. The road to better management in resistant hypertension-diagnostic and therapeutic insights. *Pharmaceutics*. 2021;13(5):714. doi: 10.3390/pharmaceutics13050714
10. Siddiqui M, Calhoun DA. Refractory versus resistant hypertension. *Curr Opin Nephrol Hypertens*. 2017;26(1):14-19. doi: 10.1097/MNH.0000000000000286
11. Eide IK, Torjesen PA, Drolsum A, Babovic A, Lilledahl NP. Low-renin status in therapy-resistant hypertension: a clue to efficient treatment. *J Hypertens*. 2004;22(11):2217-26. doi: 10.1097/ 00004872-200411000-00026
12. Buso G, Agabiti-Rosei C, Lemoli M, Corvini F, Muiesan ML. The global burden of resistant hypertension and potential treatment options. *Eur Cardiol*. 2024;19:e07. doi: 10.15420/ecr.2023.51
13. Mancia G, Kreutz R, Brunström M, et al. 2023 ESH Guidelines for the management of arterial hypertension The task force for the management of arterial hypertension of the European society of hypertension: endorsed by the international society of hypertension (ISH) and the European renal association (ERA). *J Hypertens*. 2023;41(12):1874-2071. doi: 10.1097/HJH.0000000000003480
13. Vongpatanasin W. Resistant hypertension: a review of diagnosis and management. *JAMA*. 2014;311(21):2216-24. doi: 10.1001/jama.2014.5180
14. Saneei P, Salehi-Abargouei A, Esmaillzadeh A, Azadbakht L. Influence of dietary approaches to stop hypertension (DASH) diet on blood pressure: a systematic review and meta-analysis on randomized controlled trials. *Nutr Metab Cardiovasc Dis*. 2014;24(12):1253-1261. doi: 10.1016/j. numecd.2014.06.008
15. Moser M, Setaro JF. Clinical practice. Resistant or difficult-to-control hypertension. *N Engl J Med*. 2006;355(4):385-392. doi: 10.1056/NEJMcp041698
16. Garg JP, Elliott WJ, Folker A, Izhar M, Black HR; RUSH University hypertension service. Resistant hypertension revisited: a comparison of two university-based cohorts. *Am J Hypertens*. 2005;18(5 Pt 1):619-26. doi: 10.1016/j.amjhyper.2004.11.021
17. Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension*. 2012;59(6):1104-1109. doi: 10.1161/HYPERTENSIONAHA.111.190637
18. Williams B, MacDonald TM, Morant S, et al. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug- resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. *Lancet*. 2015;386(10008):2059-2068. doi: 10.1016/S0140-6736(15)00257-3
19. Tian Z, Vollmer Barbosa C, Lang H, Bauersachs J, Melk A, Schmidt BMW. Efficacy of pharmacological and interventional treatment for resistant hypertension: a network meta-analysis. *Cardiovasc Res*. 2024 27;120(1):108-119. doi: 10.1093/cvr/cvad165
20. Georgianos PI, Agarwal R. Ambulatory blood pressure reduction with SGLT-2 inhibitors: dose-response meta-analysis and comparative evaluation with low-dose hydrochlorothiazide. *Diabetes Care*. 2019;42(4):693-700. doi: 10.2337/dc18-2207
21. DiBona GF. Sympathetic nervous system and hypertension. *Hypertension*. 2013;61(3):556-60. doi: 10.1161/HYPERTENSIONAHA.111.00633
22. Iliescu R, Lohmeier TE, Tudorancea I, Laffin L, Bakris GL. Renal denervation for the treatment of resistant hypertension: review and clinical perspective. *Am J Physiol Renal Physiol*. 2015;309(7):F583-594. doi: 10.1152/ajprenal.00246.2015
23. Rader F, Kirtane AJ, Wang Y, et al. Durability of blood pressure reduction after ultrasound renal denervation: three-year follow-up of the treatment arm of the randomised RADIANCE-HTN SOLO trial. *EuroIntervention*. 2022;18(8):e677-e685. doi: 10.4244/EIJ-D-22-00305
24. Curneen JMG, Rabbitt L, Browne D, et al. Major disparities in patient-reported adherence compared to objective assessment of adherence using mass spectrometry: a prospective study in a tertiary-referral hypertension clinic. *Br J Clin Pharmacol*. 2023;89(7):1948-1955. doi: 10.1111/bcp.15292